GENE THERAPY OF CANAVAN DISEASE

Part III-D) A one-page description of the proposed experiment in non-technical language

This protocol describes an experiment to study a gene therapy approach to Canavan Disease. Canavan Disease is a genetic disease of the brain known as a leukodystrophy which prevents the normal formation of the white matter in the resulting in profound developmental retardation and death in the first decade of life. There are no current treatments for this disease. As the gene responsible for Canavan Disease has been identified, the disease may now be considered for gene therapy. Canavan Disease is specifically attractive for gene therapy because the effect of the gene delivery can be determined using MRI and a form of MRI that measures the biochemistry of the brain, using proton spectroscopy of the brain. The acid, which is elevated in Canavan Disease, can readily be measured by proton spectroscopy and if the gene transfer is successful we would expect to see a fill in levels of this acid associated with some clinical improvement in the children. The method to deliver the gene to the brain in this study is a new form of a non-viral delivery system. This is based on a liposome, a small lipid particle, which encapsulates the Canavan gene, which has been condensed by another reagent which binds to DNA. This final complex, which we call LPD (for liposome-encapsulated, polycation-condensed DNA) can introduce genes into the brains of experimental animals and we therefore believe it may also be able to work in the human brain.

Children will undergo a baseline evaluation which will include examinations by both neurologists and neuropsychologists to get an accurate measure of their developmental age. In addition they will undergo a number of additional medical tests which include the MRI and the spectroscopy mentioned above. These tests will be repeated before surgery. The gene transfer itself will require a small operation in which the children undergo general anesthesia, the scalp opened and small hole drilled in the brain through which a fine tube attached to a reservoir inserted into the fluid-filled lakes in the center of the brain. Into this fluid (CSF), the Canavan gene in its special LPD complex will be delivered. After the operation, the children will be followed up with the same tests that were used during the baseline procedure. These evaluations will be carried out at 1,3,6, 12 months post-surgery and then at yearly intervals. A preliminary human study in two children using the same approach has demonstrated both safety and tolerability as well as some clinical and

biochemical improvements in both children. In one child, repeated MRI scans showed some increase in the myelin signal. Two children however are insufficient for us to make any conclusions, even on the safety of the reagent. We are therefore proposing to extend that study to include more children to enable us to make some conclusions about the safety of the approach and perhaps even some tentative conclusions on potential efficacy.